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Polypoid Disease of the Intestines

Its Origin, Development, Implications and Treatment

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THE STUDY OF POLYPOID DISEASE of the digestive tract has fascinated internists and surgeons for many years. Ever since the description by Menzel[24] in 1721 of a number of wartlike excrescences arising in the colonic mucous membrane which showed evidence of pronounced inflammation, investigators all over the world have been interested in this subject. A mountain of literature on it has accumulated. Most of it has dealt with the incidence of polyps, opinions about their relation to cancer, and treatment.

I shall try to present in an orderly fashion the story of intestinal polyposis as we know it today, drawing largely on my own experience and to a lesser degree on the experience of others as I have gleaned it from the literature. I shall make no attempt to bring to your attention all the opinions of those authors whose names appear in publications, although they may not be irrelevant to the subject. I should like to refer again, however, to Menzel's description of polyps, which apparently started a chain of events that brought to light so many of the problems related to intestinal polyps which have been a source of concern to many observers since.

The big problem, of course, has been the relation of polyps to carcinoma, but then there have also been the problems of the relation of inflammation to polyposis and of the relation of inflammation to carcinoma. However, it might be interesting to list a few of the outstanding names of those who have contributed to knowledge of the subject of polyposis in the last 200 years. You will probably find some names lacking, but may I remind you that I have made no effort to make a complete review of the literature, but rather am listing those whose studies have particularly influenced my views and who, I feel, have played a part in my observations in the sum total of our present knowledge of the subject of intestinal polyps. These names include Wagner, Rokitansky, Lebert, Virchow, Verse, Woodward, Cripps, Erdmann and Morris, Susman, Schmieden and Westhues, Lockhart-Mummery and Dukes, Ribbert, Hurst, Genkin and Dmitruk, Hoelzel and Da Costa, McKenney, Kennedy and Weber, Mayo and Wakefield, Ewing, Saint, Broders, Coffey, MacCarty,[20] Rankin, Robertson, Spriggs, Struthers, Swinton and Warren, Wesson, Yeomans, Cromar and Dixon,[2] Sloan and Gage, Hauch, Buie and Smith, Atwater,[1] and many others, all of whom have made substantial contributions to present-day knowledge of intestinal polyposis.

The results of earlier investigations suggested that there may be several kinds of intestinal polyps, dissimilar both etiologically and pathologically, and this undoubtedly accounts for the innumerable classifications which have been suggested in later years. There are several basic concepts concerning the etiology of multiple adenomas of the large bowel: First, the hypothesis of Virchow [38] that a hyperplastic response

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to inflammation produces the polyps; second, the opinion of Ribbert[27] that the tumors originate from misplaced embryonic rests in the wall of the bowel; third, the hypothesis that chronic irritation in the presence of a congenital predisposition is necessary, as suggested by Verse.[37] Genkin and Dmitruk,[11] as well as Hoelzel and Da Costa,[13] produced polyps experimentally in animals.

The hereditary or familial disposition to multiple adenomatosis of the intestine has been noted repeatedly by many of the authors mentioned. Lockhart-Mummery[18] expressed the opinion that the condition is transmitted as a mendelian dominant. Congenital occurrence of the polypoid disease has never been substantiated by the demonstration of polyps at birth, although my colleagues and I have seen polyps in the second year of life. Present-day knowledge and review of the literature make it obvious that the concepts of etiology expressed in the past are quite comprehensive. Whereas various observers in the past have tried to make various types of polyps conform to a pattern, subsequent experiences have shown indubitably that polyps, as they are now seen, have a variety of origins. Therefore, to get a better concept of the polyps in any individual case, it is well to have, as one might say, a bird's-eye view of the field of polyposis as a whole so that when any case is seen, the polyps present may immediately be classified and the treatment directed accordingly.

CLASSIFICATION

It is best to classify polyps (Table 1) as to their origin, inception and development, since by doing so, one will get a broader view of the subject and will be able to crystallize opinion about what to do in any given case of polyposis or intestinal polyps.

With such an outline and a good clinical history, a given case of polyps can be readily placed in its proper category. Increasing experience will continuously enhance the value of such a classification. The treatment of one type of polyposis or polyp involves eradication of the polyps. In another type, the situation is quite the opposite. There has been a great deal of misunderstanding about this in the past, and I dare say that in some cases the colon has been removed unnecessarily because of failure to comprehend the nature of some polyps. Such comprehension can only come through long experience with many cases, but a classification of this type is invaluable in arriving at a solution of any given case of polyps.

PATHOGENESIS

Opinions concerning the pathogenesis of polyps have varied greatly in the past. Here again, the various hypotheses suggested indicate that the observer advocating this or that hypothesis tried to

TABLE 1.—*Classification of polyps to suggest their origin, inception and course of development*

Group 1—Single polyps.
Group 2—Multiple polyps.
Group 3—Disseminated polyposis.
Group 4—Diffuse polyposis.
Group 5—Polyposis secondary to inflammatory disease.

catalogue all cases of polyps into a single classification as far as their origins and development were concerned. Each hypothesis has had some support in scientific observation. Each has failed to meet all the requirements of explaining the formation and growth of all types of polyps. A study of the origin of polyps is in essence the study of the formation of tumors itself. At least four pathways of origin of intestinal polyps are now well recognized.

The first deals with the commonly accepted thought that polyps begin as an overgrowth of the intestinal epithelium with the heaping of cells on cells, finally forming visible mammillations or excrescences on the surface and these in turn growing larger until they become well-recognized adenomas. Between October 1, 1942, and February 1, 1943, Atwater and I examined with a hand lens the carefully cleansed colons of all the individuals who came to necropsy at the Mayo Clinic. Of the 241 individuals examined, 166 had polyps. The study included newly born infants and adults up to 90 years of age. No polyps were observed until the fourth decade of life and the incidence was greatest in the sixth and eighth decades. The mean age of the patients who did not have polyps was 51 years, whereas the mean age of patients who did was 64 years. There were 3.18 men with polyps to each woman. However, since the same proportion of men to women existed in the control group, the sex distribution would hardly seem significant. In no instance was a mucosal projection considered a polyp unless there was adequate microscopic verification. This study showed that in polyps there was thickening of the mucosa owing to the elongation of the crypts of Lieberkühn.

From this study it seems highly likely that the epithelium of the colon must pass through a chain of changes in the development of polyps. The primary change is epithelial. The reason, however, why a localized patch of epithelium undergoes aberration from the normal is not evident. However, the existence of morphologic changes of varying degrees is apparent. The genesis of a polyp is recognized earliest on the basis of more rapid proliferation of the epithelium at one site than in the neighboring epithelial elements. It is possible that this ability to proliferate is inherent in normal epithelium. If so, it would seem that some restraint or some inhibitory factor had been removed or diminished and thereby

an indefinite degree of overgrowth had been made possible. At times, such changes proceed to the point of pedunculation of the mucosa, possibly designed to afford a greater base and easier nutritional supply to the growing structure. When this occurs, the pedunculated and so-called benign polyp is formed. The epithelium in the glands when the polyps first begin to develop exhibits primary hyperplasia. The cells retain their normal microscopic appearance and their apparent physiochemical functions such as production of mucus.

The numerical increase results in enlargement of the size of each crypt of Lieberkühn involved in the proliferative process. In order to accommodate for this increase, the glandular structure itself must elongate. Limited by the muscularis mucosae and the subepithelial structures, this growth proceeds toward the lumen of the intestine. Such glandular hypertrophy becomes evident in a localized region within which the glands are taller and deeper than the neighboring normal structures. A tiny plaque or elevation is produced on the mucosal surface of the bowel. From the observations in this study other changes then follow.

In the process of accommodation of the overgrowth the tubules often become branched and the nuclei pile on each other. They lose their normal position near the membrana propria and move outward toward the lumen of the tubule. An increasing proportion of cytoplasm appears between the nucleus and base of each cell. The outline of the nuclei changes. The nuclei lose their cuneiform shape and become spherical. Polyhedral, irregular nuclei are prominent. The chromatin content of the nuclei increases in many cells. In others, the vesicular character becomes evident. Mitotic figures become more frequent. The columnar shape of the individual cells gradually is lost and a more cuboid form is assumed. Cells lose their normal alignment and eventually become a heterogeneous group with no regularity of position. The alignment of the glands becomes irregular. The ability of the cells to produce mucus is gradually lessened. If simple hyperplasia only is present, as it is at this stage, staining usually is like that of normal cells. However, a small percentage of benign polyps display variation in their ability to be stained by hematoxylin and eosin.

At the site of the primary hyperplasia in the benign polyps, the basement membrane is intact. Minimal changes are noted in the mucosal stroma until the larger polyps have been formed. At that point, the polyps are frequently the seat of inflammatory changes and small hemorrhages. The presence or absence of these changes forms a pattern. This pattern depicts an epithelial transition progressive from normal tissue to the so-called benign polyps through the various degrees of cellular differentiation. From all of this, it becomes evident that at least one way in which polyps are formed is through epithelial changes.

Another way in which polyps develop is through changes in the muscularis mucosae and the lymphoid tissue, namely, the subepithelial structures. The amount of lymphoid tissue in the subepithelial layers is variable in the colon of humans. The lymphoid tissue occurs as aggregations of lymphocytes situated immediately below the epithelial layer. These lymphoid aggregations may occur as perivascular infiltrations about the blood vessels and they may lie either superficially to or deeper than the muscularis. The size of the individual lymphoid aggregations also varies. When a lymphoid aggregation becomes very large, it disrupts the continuity of the muscularis mucosae. Under pathologic conditions it may become encapsulated and acquire well-marked secondary centers which show up as a collection of large, pale-staining cells in the center of the lymph follicle. When this stage has been reached, secondary changes become evident in the overlying epithelium. Encapsulated follicles with secondary centers rarely, if ever, occur in a normal colon.

Our observations in this regard concern a group of 61 patients with carcinoma of the colon, 2.5 cm. in diameter or less, coming to the Mayo Clinic between the years 1909 and 1934, inclusive. The investigation was prompted by a discussion of the advisability of extensive and radical resection for such small lesions. The lesions varied from 0.5 to 2.5 cm. in diameter. The average was about 1 cm. In all the patients, apparently a single carcinoma was found both clinically, preoperatively, and at operation. In 26 of the 61 patients the lesions were situated within approximately 5 cm. of the anus. Fourteen of the patients had a grade 1 lesion, 34 had grade 2, ten had grade 3, and three had grade 4. Twenty-eight (46 per cent) lived more than 5 years after operation. Thirty-four of the 61 at the time of resection showed no extramural spread. In 27 of these 34 instances, there was extramural spread of the tumor following operation and in 14 of the 34 there was local invasion beyond the intestinal wall. Since the growths were 2.5 cm. or less in diameter the question naturally arose, why were not the end results better?

The operation used was as radical as those commonly done in surgical treatment of lesions much larger than the average size of lesions in this group. Thus, the small size of the lesions in this group was not a prominent factor in determining the ultimate results as far as cure or further development of carcinoma was concerned. Nor did the type of operation used for any individual growth constitute

a determining factor in the ultimate result. The site of the lesions, the grade of malignancy, the type of lesion according to infiltration of the wall, extramural spread, involvement of the lymph nodes, and age of the patient at onset seemed to be vital prognostic factors. The number of carcinomas which developed when there had not been extramural spread at the time of resection was somewhat unexpected. The occurrence of new growth, after apparently complete surgical ablation, suggested that the causative factor may reside not in the epithelial cells of the growth itself, but in the surrounding tissue.

MacCarty[21] had previously stressed the significance of the environmental relations of various cells and had drawn particular attention to the influence of lymphoid tissue on the nutrition of epithelial cells. For this reason a detailed histologic study of the surrounding tissues of these cancers was made. From this observation, it became apparent that in many cases one is not dealing with recurrence of a removed carcinoma but that a new carcinoma separate and distinct from the original growth has caused death. A careful study of the submucosal structures of these specimens showed large encapsulated lymph follicles with well-formed secondary centers in all but one of the cases. That particular case was one in which the carcinoma had arisen in a diverticulum. Changes in the epithelium were seen when the follicles were fully developed and contained secondary centers.

One wonders if the epithelial changes were not secondary to or the direct result of the underlying follicles. Rupture of the follicle would allow the epithelium to prolapse into the submucosa. The subsequent fate of the prolapsed epithelial cells would appear to be governed by the extent of the lymphatic barrier which surrounded them. Occasionally, the follicles ruptured into the lumen of the bowel, causing ulceration. In the process of the healing of the ulcers thus formed, epithelial cells became trapped in the deep layers of the base of the ulcer. Occasionally a small patch of epithelium became isolated from the rest of the stratum by a circle of large follicles. Progressive enlargement of these follicles seems to destroy the muscularis mucosae and the epithelium becomes pegged down. Subsequent change consists of irregular hyperplasia of the glandular structures of the isolated portion of the mucosa. By the continuation of this process the cells become more primitive in type with changes taking place in the epithelium. Traction, possibly by the passage of fecal material over the surface of the epithelium, causes the structure to become elongated and extrude farther into the intestinal lumen. In this way, a more or less definite polyp would form.

These observations show the changes that occur in the tissue surrounding a cancer of the colon. The changes consist primarily of the enlargement of the lymphoid aggregations in the submucosa with resultant damage to the muscularis mucosae. The subsequent development of large encapsulated follicles with secondary centers produces associated changes in the epithelial cells. How frequently the pathogenesis of polyps occurs in this manner, of course, it is hard to say.

The third and commoner and more clearly understood way of the development of polyps is that following such an inflammatory disease as ulcerative colitis. This, as you know, can be a devastating and destructive disease. In the severe and destructive disease, the mucous membrane looks as if it were literally torn to shreds and tatters. Often I have inserted my finger into the rectum of patients with ulcerative colitis in whom it was difficult to find the actual lumen of the bowel, there being so many side passages where the mucosa had been deeply ulcerated and denuded. The whole lining of the large intestine may be similarly affected, as attested by carefully done roentgenologic examinations. As the healing then proceeds, there develop curled-up mucosal tags and bits of mucous membrane, largely represented by granulation tissue. Sometimes these tags are attached at both ends, forming bridges, and generally, except for the destruction between them, resembling grossly the appearance of polyps.

Polyps that follow ulcerative colitis can be classified into three types: Pseudoadenomatous, adenomatous and carcinomatous. Microscopically, the polyps vary in size from a few millimeters to as much as 3 cm. or more in diameter. They appear as protruding tufts of mucosa in areas that are otherwise devoid of any mucous membrane. They occasionally have the appearance of exuberant outgrowths from the already diseased mucosa.

In the so-called pseudoadenomatous polyps, there are structures ranging from small tags of granulation tissue with more or less complete absence of mucosa, to large pedunculated polyps several centimeters in diameter, composed largely of hyperplastic glands. The important criterion in this classification is not the amount of glandular tissue in the polyps, but rather the cytologic structure of the individual gland. The polyps often appear adenomatous at first glance, but on more detailed scrutiny glandular hyperplasia is recognized as a benign, regenerative process. This is evidenced by the orderly arrangements of the lining cells in which the normally staining nuclei are lined along the basement membrane with an overlying layer of clear cytoplasm. Frequently in them, large cystic glands are seen. In other words, some of the pseudoadenomatous polyps are hyperplastic, but their hyperplasia is an orderly

functional response to the underlying stimulus, inflammation. The term "pseudoadenomatous" is applied to this group to indicate that evidence of tendency toward neoplastic change is lacking. This is the group frequently called "pseudopolyps" of colitis.

In the second group, adenomatous hyperplasia is recognized. In these, the size ranges from small fingerlike projections of granulation tissue containing only a few glands to large pedunculated and sessile polyps. They usually are larger and possess a more exuberant character than the pseudoadenomatous polyps, but exceptions to this are noted. Adenomatous changes in the glands are manifested by increase in size, abnormally deep staining and malalignment of the nuclei, numerous mitotic figures, diminution of the amount of the cytoplasm, and diminution of the amount of mucus produced. At times, these changes are slight and are distinguished with great difficulty from the more advanced types of pseudoadenomatous hyperplasia.

On the other hand, advanced adenomatous hyperplasia involves a fine distinction from carcinoma in situ. Carcinomatous polyps are usually relatively larger than adenomatous polyps. They present a dusky red, hemorrhagic appearance, which immediately arouses suspicion of their malignant nature. However, in some instances, carcinoma in situ is discovered in small adenomatous polyps. Thus, we have polypoid structures resulting from extensive inflammation and destruction of mucous membrane. In some cases, and in fact in most, these polyps are only the tags of mucous membrane remaining after denudation of most of the mucosa. As healing occurs, they retract and eventually become smaller. There are, however, exceptional polyps in which adenomatous and finally carcinomatous change may occur. It is most important that these two groups of polyps be differentiated carefully, by macroscopic and sometimes by microscopic examination.

A fourth factor to be considered in the pathogenesis of polyps of the intestine is the hereditary or familial factor. Cripps[7] is credited with recording the first observation that two members of the same family might have polyps of the rectum. Since this report, many isolated family histories have been recorded. Some of these reports have involved two or three members of one generation or two or three generations who have had polyps of the colon. Such reports, of course, are of limited value, but they hint at the familial origin of polyps. Even larger families, as the one which I shall show in this report, are of little value as far as human genetics is concerned. They are of limited value principally because family histories are notoriously inaccurate and not often can enough information concerning the general health of the family be obtained. The family on which data were collected by my colleagues, Friedell and Wakefield,[10] is illustrative of the point. Their data, as well as reports of many similar families collected from all over the world, indicate that this is a hereditary factor as far as the occurrence of polyps of the large intestine is concerned. These polyps are epithelial proliferations which are potential carcinomas. My colleagues and I have collected data on numerous such families and we have followed some of them through three, four or five generations. We have found, for instance, that one German forebear, whose descendants settled in Winona, Rochester and St. Paul, Minnesota; Milwaukee, Wisconsin; Cincinnati, Ohio, and several other German communities, left progeny in whose families several and sometimes many members developed polyps. These families can be definitely traced through three and four generations to this German ancestor. It was relatively easy to make family trees of this family up to and through these four generations. They yielded a striking illustration of the importance of the hereditary factor.

When this hereditary factor is present, the tendency is transmitted by both males and females, a fact which is shown in the case which I am illustrating. Inheritance has been traced through several generations. However, about half of the patients with this disseminated polyposis who have been seen at the Mayo Clinic have not had this hereditary factor, or at least it could not be ascertained. When the hereditary tendency does exist, it does not produce any known genetic pattern. It is not sex-linked, and is neither a mendelian dominant nor a recessive. These observations are of interest but rather tend to minimize the importance of the familial or hereditary factor. They do stress, however, that this factor is of importance in a substantial number of cases. In some families, this factor presents a most striking illustration of the value of careful inquiry into the family history.

LOCATION OF POLYPS

A few words should be said about the location of polyps of the intestine. It is readily understood that the polyps of the familial type are disseminated polyps or represent so-called diffuse polyposis. At times, those which are multiple may be found in any portion of the large intestine, and sometimes cover the entire mucous membrane so that one may speak of polyposis *en nappe* just as one speaks of this in the stomach. This is a condition in which the entire mucous membrane is more or less polypoid. In the polyposis secondary to ulcerative colitis, the polypoid changes may be disseminated throughout the large intestine; but even in this, inasmuch as the disease is more severe and more prevalent in the

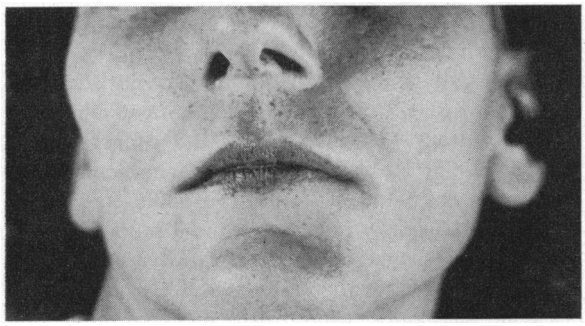

Figure 1.—Unusual pigmentation of the lips of a patient with polyps disseminated throughout the digestive tract.

distal than in the proximal segment, so too the secondary polyposis is commoner there. However, except for these conditions, the polyps of the large intestine are inclined to occur in the rectum and sigmoid portion of the large intestine, so that the vast majority of them can be felt with a finger or seen through a sigmoidoscope. The location is similar to that of frank carcinoma, which occurs well within the reach of a sigmoidoscope in about 70 per cent of the cases.

There is, however, another type of adenomatous polyp which may occur anywhere in the intestinal tract, from the duodenum down to the anus. It is associated with other rather unusual changes. The condition is rare. The polyps are inclined to occur in the small intestine, although they may occur at any point of the intestinal tract. They may even occur in the stomach. It is a condition quite different from the so-called familial polyposis, although the disease seems to be hereditary and many members of the same family may be involved.

The history is usually that of a young adult who has intermittent colicky, abdominal cramps, or even episodes of intestinal obstruction, sometimes associated with rectal bleeding and vomiting. Associated with these symptoms, there is an unusual pigmentation of the skin, particularly of the mucous membrane, lips (Figure 1), tongue and cheeks. Peutz,[25] of Holland, described the condition and Jeghers, McKusick and Katz[15] of this country described it in more detail in 1949. The condition has come to be known as "Jeghers-Peutz syndrome." Up to 1955, fewer than 30 cases of the condition had been reported in the literature. My colleagues and I have not seen more than four or five patients with the disease at the Mayo Clinic. Of course it is quite possible that the condition was overlooked in the past. It seems obvious that the condition is one definitely at variance with so-called familial polyposis.

Polyps of the small intestine, in general, are very rare. This is in line with the relative rareness of neoplastic lesions of the small intestine generally. Parenthetically, I might say that in a ten-year period during which we saw 5,900 cases of carcinoma of the stomach and 7,200 cases of carcinoma of the large intestine, we saw only 132 cases of carcinoma of the small intestine at the Mayo Clinic, and I believe that the relative ratio of adenomatous polyps in the small intestine is similar to that of carcinoma.

INCIDENCE

Many observers have reported on the incidence of polyps of the intestine. Most of the data have been on the basis of necropsy reports. Unfortunately these examinations were not divided according to age groups and so the incidence has been reported far too low. In the series of 241 cases, previously mentioned, in which the colon was examined postmortem by Atwater and myself,[1] there were polyps in 166, an incidence of 69 per cent. This, of course, is much higher than we had expected or than any that had been previously reported. I mentioned before that no polyps were observed until the fourth decade of life and the appearance was most frequent in the sixth and eighth decades. This would make it obvious that polyps of a single or multiple type are inclined to occur in the older age group.

It is obvious and many investigations have proved that a person often has adenomatous lesions of the colon without having symptoms. My colleagues and I undertook an investigation in 1948 to obtain information regarding the value of routine proctosigmoidoscopic examination. This study was conducted by Hauch, Buie, Smith and myself[12] over the period from April 6, 1948, to January 6, 1950, inclusive. During this time, proctosigmoidoscopic examinations were conducted on 2,161 patients from two of the sections of internal medicine at the Mayo Clinic, a section which deals chiefly with enterologic conditions and a section where attention is given, regardless of the nature of the complaints, to patients who live in the immediate vicinity of Rochester. The former dealt with patients who often complain of gastrointestinal conditions and the latter with patients of the type usually seen in a general medical practice. None of the 2,161 patients who formed the basis of our investigation had any symptoms referable to the intestine, such as bleeding, diarrhea, hemorrhoids, abdominal cramps, or change in bowel habits. However, on careful analysis of the records at the end of the 21 months, it was found that only 1,919 were entirely free of symptoms referable to the colon and rectum. The incidence of rectal and sigmoidal adenomas among the 1,919 patients who had no symptoms referable to the colon and rectum was 8.1 per cent. When these patients were grouped according to age, it was observed that there was a progressive rise in the incidence of adenomas from

the second to the eighth decade of life. It was also found that the incidence of these polyps was twice as great among men as among women.

Of the 156 patients who had adenomas, 119 had solitary lesions and 37 had more than one. Of the solitary adenomas, 57 per cent were found in the sigmoid and 33 per cent in the rectum. The diameter of all but ten of the growths was less than 1 cm. Among the larger adenomas, examined histologically, the pathologist reported "low-grade 1 adenocarcinoma in an adenoma." This study brings to our attention the fact that beyond the age of 30 years there is an increasing incidence of rectal and sigmoidal adenomas.

In patients with diffuse polyposis the situation is quite different. Since an appreciable number of these patients (at least one half according to our calculations and observations) are born with the hereditary tendency to polyposis, the mucosal change occurs somewhere in the first or at least in the second decade of life. How long such patients go about with polyps in their intestines before they seek the aid of a physician, of course, is unknown, but the common time when they come for help is in the third decade of life. They come because of rectal bleeding. This may be due to one of two causes, either a simple irritation of the adenomatous polyps or the development of carcinoma. The latter is the likely occurrence. Commonly when these patients are first seen and examined, carcinoma is already present. Frequently, there are more than one, and often, many. Thus, the incidence of these polyps in contrast to the single or multiple adenomas is in the early years of life.

In the case of the polyps occurring in patients with ulcerative colitis, the situation is somewhat as follows. The disease commonly occurs in the second and third decades of life. It may be very severe, or fulminating, and when it heals the mucosal tags known as polyps are left in its wake. These polyps usually occur in the second and third decades of life.

DEVELOPMENT OF CARCINOMA

The determination as to whether or not a lesion which is diagnosed as entirely benign may ultimately become malignant rests on clinical grounds alone. There is no good method based on morphology alone which will determine whether a benign neoplasm will develop malignant characteristics in the years to come. I shall use the term "precancerous" advisedly for this reason. However, the accumulative evidence that an adenomatous polyp can develop into a carcinoma is so overwhelming that it is difficult of denial. The transition from benign to malignant has been traced and seems now to be an actuality rather than an unsupported hypothesis. It would be a nearly impossible task to determine the course of an individual adenoma of the large bowel without repeated observations of its change from adenoma to carcinoma.

As long ago as 1935, Buie and Brust reported data on a group of 143 patients with polyps of the rectum and rectosigmoid discovered by sigmoidoscopic examination. In those days the importance of destroying all of these polyps by electrocoagulation was not as evident as it is today and 87 of the 143 patients did not have this treatment. Fifty-five of these 87 patients were examined again after an interval of five or more years. In three, the untreated adenoma was found to be larger at the second examination than at the first. In four, there was a carcinoma at the exact site of the previously noted adenoma. Here there were four instances of apparent transition from apparent benign to outright malignant growth. I looked up the record of one of these patients. He was examined at the age of 60 years in 1926, at which time a polyp 4.5 by 2 cm. in size was observed at 12 to 13 cm. above the pectinate line. On the second examination in September, 1949, a rather large carcinoma at this site was noted. A specimen removed from this showed it to be an adenocarcinoma, grade 2.

When a diagnosis of diffuse or familial polyposis is made, it is customary to inquire into the family history of the patient. If he has children or brothers and sisters who are asymptomatic, they are advised to undergo proctoscopic and roentgenologic examinations of the colon. Not infrequently the same condition is found in these relatives. If they are children in the first decade of life, they probably have no symptoms, and the polyps are of a benign adenomatous type. However, in the second or third decade of life, symptoms develop. Frequently in patients of that age, at the time of the removal of the colon it will be found to have multiple carcinomas in the field of diffuse adenomatosis. I have spoken of the three types of polyps occurring in the wake of ulcerative colitis. The malignant type is very rare, but I believe that at this point it is well to make some comments on the incidence of carcinoma in ulcerative colitis. How frequently this eventuates through the course of adenomatous polyps it is difficult to say, but its occasional occurrence is apparent.

We have studied data on a group of 2,000 patients with chronic ulcerative colitis who were examined at the Mayo Clinic between January 1, 1918, and December 31, 1937, inclusive. Of these, 1,564 patients[3] were less than 50 years of age at the time of diagnosis of chronic ulcerative colitis at the clinic, had been traced for a year or more after the diagnosis had been made, and had been free of malignant lesions for at least a year. Of these 1,564 patients, 98 had died of carcinoma, as compared with 27

TABLE 2.—*Chronic ulcerative colitis: Comparison of observed deaths from malignant neoplasm of the colon with expected deaths in the general population**

Age at Diagnosis, Years	Traced Patients	Person-Years Exposed	Expected (E) Deaths†		Observed (O) Deaths: Malignant Neoplasms of the Rectum and Colon	Ratio of Observed to Expected Deaths	
			Total Malignant Neoplasms (E-1)	Malignant Neoplasms of Digestive Organs and Peritoneum (E-2)		O:E-1	O:E-2
2 to 4	8	132.5	0.010	0.001	1		
5 to 9	25	304.0	0.025	0.002	5	85.5	650.0
10 to 14	65	863.5	0.117	0.017	7		
15 to 19	127	1,424.5	0.280	0.050	12	42.9	240.0
20 to 24	219	2,609.5	0.938	0.208	11	11.7	52.9
25 to 29	294	3,945.5	2.845	0.767	17	6.0	22.2
30 to 34	301	3,911.5	4.478	1.342	15	3.3	11.2
35 to 39	229	3,151.5	5.746	1.930	9	1.6	4.7
40 to 44	166	2,144.5	5.702	2.107	15	2.6	7.1
45 to 49	130	1,738.5	6.631	2.676	6	0.9	2.2
Total	1,564	20,225.5	26.772	9.100	98	3.7	10.8

*Reproduced by permission from Gastroenterology, 26:32, Jan. 1954.
†Expected deaths calculated from U. S. death rates for 1949 in Vital Statistics.

expected deaths from malignant neoplasms of all sites and nine expected deaths from malignant neoplasms of digestive organs and peritoneum (Table 2). Obviously, the expected number of deaths from malignant neoplasms of the rectum and colon is less than nine, say three or four deaths; on this basis, the ratio of observed to expected deaths would be about 20 or 30 to one.

The impressive data of this study do not concern themselves with the total number of patients with cancer, but rather with the fact that the cancer occurred in patients with ulcerative colitis on the average 20 to 30 times more frequently than in members of the general population of similar age groups. One must remember, however, that this frequency is greatly increased by the fact that in 13 patients of this group carcinoma developed before the age of 15 years, which is an age when carcinoma almost never occurs in ordinary persons. If these 13 are taken from the list, the ratio of observed to expected is somewhat reduced. It must further be recognized that the average patient with chronic ulcerative colitis in this series was 31 years of age and he had a better than 50 per cent chance of living 25 years. It is not known in what percentage of these patients the development of the carcinoma went through the stage of adenoma and carcinoma subsequently, but it would be safe to assume that the number taking that course was small. Carcinoma in these patients is inclined to develop in a very different manner.

TREATMENT

This rather gloomy story of polyps, from the standpoint of frequency, the limited possibility of early detection, and the considerable possibility of eventuation into carcinoma, should stimulate clinicians and surgeons to devise ways and means of diagnosing these lesions in their incipiency. Once the diagnosis is made, the treatment is very satisfactory. This is in rather sharp contrast to so many other conditions coming to the attention of physicians, in which diagnosis may be made readily enough but satisfactory treatment is not at hand. In the discussion of polyps, the situation is quite the reverse and treatment can be outlined in a few words. When an adenomatous polyp is discovered, it should be destroyed. When the polyp is single or when only a few are present, and when they can be visualized through a sigmoidoscope, simple electrocoagulation is the treatment of choice. When they are found roentgenologically and there are many of them, subtotal colectomy and ileosigmoidostomy or ileoproctostomy are the procedures of choice. The remaining polyps in the rectum and in the field visible through a sigmoidoscope can be destroyed after the major operation is completed. If one or two polyps are discovered roentgenologically, removal by transcolonic excision is frequently all that is necessary. This is certainly preferable to subtotal colectomy if that operation can be avoided.

And now we come to that subject which still represents some controversial features, although the latter should not be so: Namely, the subject of the polyps occurring in the wake of ulcerative colitis. In some of these cases, ileostomy and colectomy will be the treatment of choice. In the majority, this will not be so. Most of the polyps, as was indicated before, occurring in the wake of ulcerative colitis are simply mucosal tags which, as the disease heals, shrink to a smaller size and sometimes to obscurity. However, the patient who has recovered from ulcerative colitis and who has polyps after the bowel has healed should be examined from time to time. I have made

it a custom to do this every six months until the patient is symptom-free.

I have some patients, one man in particular, who have the entire lining of the bowel studded with these mucosal tags. I have seen this man periodically for 25 years. In the particular case mentioned there are no signs or symptoms of development of any change, except that the tendency has been for these polyps to become smaller. An illustration of this kind brings home dramatically the fact that not all patients with polyposis secondary to ulcerative colitis should undergo colectomy. In our rather extensive experience with ulcerative colitis, I have yet to see the first patient who would prefer ileostomy to the form of bowel function by the normal passage. Ileostomy is an operation which affords unpleasant handicaps, handicaps which are accepted when they are necessary, but which nobody cares for unless they are necessary. In many of these patients when the rectum heals, the mucosal tags can be fulgurated in anticipation of more major operation later. In some of these, we have been able to perform ileosigmoidostomy later when there was some change in the polyps proximal to these points. Most patients with mucosal tags or so-called polyps of ulcerative colitis are better observed once they are symptom-free.

While the treatment of polyposis is relatively well standardized, its success will be proportional to the judgment of the physician making the decisions about appropriate treatment.

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